comprising the steps of (a) forming a mixture of a sample of said fluid with (1) an amount of a specific antibody for the free portion of testosterone insufficient to substantially affect said equilibrium and (2) a labeled analog of testosterone which is radioiodinated 6-hydroxy-testosterone-19-carboxymethyl ether histamine that binds to said antibody and has affinity for the endogenous binders lower than that of testosterone for said endogenous binders, (b) maintaining said mixture to permit said labeled analog to compete with the free testosterone for binding with the antibody, (c) measuring the amount of said labeled analog that has, or has not, become bound to the antibody, and (d) determining the concentration of the free testosterone from said measurement, wherein the improvement comprises including in the mixture an amount of a blocking agent which is sulfobromophthalein to inhibit the binding of said labeled analog to the endogenous binders without displacing testosterone bound to said endogenous binders.

REMARKS

Reconsideration is requested.

Claim 55 is pending.

Paragraphs 1 through 8 of the Office Action do not appear to call for any response at this time.

Paragraphs 9 and 10 are understood to be interrelated. The Examiner objects in

paragraph 9 to prior claim 54, as containing "new matter" and in this connection, refers to paragraph 8 of the prior Office Action of September 4, 2001. At this point, it is not clear what the alleged new matter is. Perhaps we may assume that if the same or parallel language was selected and recommended by the PTO in establishing the Count in Interference No. 101,933, the language was (and is) not "new matter".

For convenience, we reproduce the language of new claim 55 side-by-side with the Interference Court, using underlining in lieu of the Examiner's italics, and underlining the common words in both claims.

Claim 55	Interference No. 101,933 Count 1
55. A method for determining the concentration of the free portion of testosterone ligand in a biological fluid, wherein said free testosterone is in equilibrium with another portion of testosterone bound to one or more endogenous binders in said fluid comprising the steps of (a) forming a mixture of a sample of said fluid with	"In a method of determining the concentration of a free portion of a ligand in a biological fluid, wherein said free ligand is in equilibrium with another portion of the ligand bound to one or more endogenous binders in said fluid comprising the steps of (a) forming a mixture of a sample of said fluid with
(1) an amount of a specific antibody for the free portion of	(1) an amount of a specific binder for the free ligand insufficient to

testosterone insufficient to substantially affect said equilibrium, and

(2) a labeled analog of testosterone which is radioiodinated 6-hydroxy-testosterone-19-carboxymethyl ether histamine that binds to said antibody and has affinity for the endogenous binders lower than that of testosterone for said endogenous binders,

(b) maintaining said mixture to permit said labeled analog to compete with the free testosterone for binding with the antibody,

(c) measuring the amount of said labeled analog that has, or has not, become bound to the antibody, and

(d) determining the concentration of the free testosterone from said measurement, wherein the improvement comprises including in the mixture an amount of a blocking agent which is sulfobromophthalein to inhibit the binding of said labeled analog to the endogenous

substantially affect said equilibrium, and

(2) a labeled derivative of the ligand that binds to said specific binder and has affinity for the endogenous binders lower than that of the ligand for said endogenous binders,

(b) maintained (sic) said mixture to permit the ligand derivative to complete with the free ligand for binding with the specific binder,

(c) measuring the amount of ligand derivative that has, or has not, become bound to the specific binder, and

(d) determining the concentration of said free ligand from said measurement, wherein the improvement comprises including in the mixture an amount of a blocking agent which substantially reduces the binding of the ligand derivative to the endogenous

binders without displacing testosterone bound to said endogenous binders.

binders without substantially reducing the binding of the ligand to said endogenous binders."

The Examiner will appreciate that testosterone is the "ligand". Of course, the "antibody" is the "specific binder", and the other specific reagents recited in claim 55 are self-explanatory by the terms found in the text of that claim.

The italicized words in paragraph 9 of the Office Action are also found in the Interference Count. The nexus between these words and the Specification disclosure of the specific species forming the subject matter of amended claim 55 has been explained in our earlier Remarks, communication filed March 15, 2002 (and not commented on by the Examiner in the recent Office Action) which we reiterate.

> "The invention of this claim resides in the use of sulfobromophthalein as a blocking agent to reduce the binding of the labeled analog ("analog tracer") or derivative, which is specified in the claim to be radioiodinated 6-hydrozy-testosterone-19-carboxymethyl ether histamine, to the endogenous binder (primarily, albumin) naturally present in the sample. The Examiner will appreciate that the cited passage discloses a free testosterone measurement or assay in a biological fluid which relies on competitive binding between free testosterone and the specified radiolabeled testosterone analog to an antibody. There exists a natural equilibrium in the patient sample between free testosterone and testosterone bound

to endogenous binders. The Examiner also will appreciate from reading pages 25-27, that if the labeled testosterone analog is able to bind with endogenous binder, a false measurement of free testosterone will result. However, when sulfobromophthalein is present as a blocking agent, the blocking agent inhibits the binding of the radiolabeled testosterone analog (analog tracer) to the endogenous binder (primarily, albumin) without displacing testosterone naturally bound to the endogenous binder. This method as recited in the claim closely tracks the disclosure at pages 25-27. Specifically, the last or "improvement" clause is directly based on Specification at p. 26, Table 21 which recites:

". . . since sulfobromophthalein inhibits the binding of the analog tracer to albumin without displacing testosterone bound to albumin."

It is sincerely submitted that the claim is well grounded in the Specification and there is not new matter."

There is no "new matter" in claim 55 and the rejection should be withdrawn.

In the Office Action, paragraph 10, the Examiner claims that "substantially affect" is indefinite. This language also appeared in the Interference Court. It is not indefinite. See York Products Inc. v. Central Tractor Farm and Family Center, 40 USPQ2d 1619 (Fed. Cir. 1996) where, in connection with the word "substantially", the Court said:

"Ordinarily, therefore, "substantially" means "considerable in . . . extent,"

American Heritage Dictionary Second College Edition 1213 (2d ed. 1982), or "largely but not wholly that which is specified," Webster's Ninth New Collegiate Dictionary 1176 (9th ed. 1983)."

The Court grasped the meaning of the word "substantially" and recognizes that its use fulfills an important function in providing some allowable latitude in the claim language. Moreover, the word is literally used all the time in chemical and biological patent claims. There is no apparent reason to endeavor to create new law in the present case.

The rejection as indefinite should be withdrawn.

The claim is rejected in paragraph 11 as indefinite in the recitation "displacing". Here, the Examiner states:

"The earlier part of the claim recites two types of testosterone, a free portion of testosterone and another portion of testosterone. It is unclear which testosterone does the above-identified limitation represent".

The answer is that the "displacing testosterone" in claim 55, penultimate line refers to the portion of testosterone bound to one or more endogenous binders. The last line of claim 55 when read as a whole makes this unescapably clear by reciting "without displacing testosterone bound to said endogenous binders" (emphasis added)

The rejection as indefinite in paragraph 11 should be withdrawn.

In paragraph 12, prior claim 54 was rejected as unpatentable over the Count of Interference No. 101,933. The Examiner states that claim 54 is subgeneric to the Count. While this is so, it does not make claim 54 or new claim 55 obvious over the count of Interference No. 101,933. It has often been the case that a species is patentable over a prior known genus.

Claim 55 is a very specific and preferred embodiment based upon a combination of recited active ingredients. This combination was NOT anywhere involved in the Interference and was not present in any of the claims rejected over the Count of the Interference (Claims 1 to 27 of US Patent Application Serial No.06/784,857). Consequently, the Board of Patent Appeals and Interferences did not and could not have ruled on the patentability of the subject matter of claim 55 to the present applicant. Likewise, this combination was not presented or involved in the Appeal to the Board of Patent Appeals and Interferences in parent Patent Application Serial No. 07/303,712 wherein the Board affirmed the rejection of other and different claims - see the Board decision dated January 9, 1998. The Interference and subsequent Appeal are irrelevant to claim 55 which was not presented on the Appeal and was not and could not have been presented in the Interference because the other parties to the Interference could not have "made" such a count, see below.

If claim 55 is to be rejected, it is incumbent for the PTO to cite prior art which renders

the subject matter of claim 55 obvious. The obviousness of other claims involved in the prior proceedings does not establish the obviousness of claim 55.

Further, Interference No. 101,733 was a four party Interference involving the present applicant in US Patent Application No. 06/784,857, Bienhaus, US Patent Application Serial No. 06/726,466, Buehler et al US Patent Application Serial No. 06/937,963 and Midgley US Patent Application Serial No. 06/704,095. A careful reading of the Bienhaus, Buehler et al and Midgley patent applications establish that none of these patent applications disclosed the subject matter of claim 55, and consequently, that claim could not have been involved in the Interference. While there is a rich and lengthy history in the present case, it is simply not germane to the patentability of claim 55.

The Examiner is correct that claim 55 does not recite an affinity constant for the specific binding ligand "up to at least 5 x 10^5 l/mol". This limitation was in support of a generic claim recitation of the specific binding ligand. The limitation served to define an entire class of specific binding ligands. This limitation would be surplusage in claim 55, however, which specifically recites that the ligand is testosterone and the specific binder is a specific antibody for free testosterone. Antibody specific to free testosterone is very well known and was known prior to this invention. While the antibody is selected based on a binding affinity constant conforming to the above-noted numerical range, there is no need to refer to it in the claim.

These comments are also applicable to the rejection of paragraph 13 of the Office

Action which asserts a "public use and sale" bar. There is no evidence anywhere in the record of a "prior" public sale or use of the specific testosterone assay, as defined by the combination of ingredients specified in claim 55. The only prior sales we know of are discussed in the Declaration of Said El Shami filed herein on or around March 9, 1998, and also in Interference No. 101,733 on January 26, 1990.. The Declarations discuss only T3 and T4 assays. It was on the basis of the inclusion of T3 and T4 assays in the Interference Court, that the Count and El Shami claims 1 to 27 were held by the Board of Patent Appeals and Interferences to be unpatentable under 35 USC 102/103, see paper issued by the Board on April 3, 1990. If the Examiner knows of any relevant "prior" sales or uses of the testosterone assay defined by claim 55, it should be made of record.

The rejections of paragraphs 12 and 13 should be withdrawn.

We have reviewed the newly cited prior art (Paragraph 14). This prior are does not add anything of significance to the issues raised in the Office Action.

The Notice of Allowance is in order.

Respectfully submitted,

Date: June 19, 2002

Joseph E. Mueth
Reg. No. 20,532

225 South Lake Avenue
Eighth Floor
Pasadena, California 91101
Telephone: (626) 584-0396